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Lewis J Kreisler
Legal Department
930 Clopper road
Gaithersburg, MD 20878

11/05/2007

EXAMINER

ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
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1645

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/664,444

Applicant(s)

BELL ET AL.

Examiner

Robert A. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17, 19 and 24-63 is/are pending in the application.
- 4a) Of the above claim(s) 2-4, 14-17 and 38-63 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 6-13, 19 and 24-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10-6-07 (2) and 10-24-07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-2-2007 has been entered.

The amendment and response filed on 8-2-2007 are acknowledged. Claims 6-7, 12-13, 24-31 and 34-35 have been amended. Claim 5 has been canceled. Claims 1-4, 6-17, 19 and 24-63 are pending. Claims 2-4, 14-17 and 38-63 remain withdrawn from consideration as being drawn to non-elected inventions. Claims 1, 6-13, 19 and 24-37 are currently under examination.

Information Disclosure Statement

The Information Disclosure Statements filed on 10-6-2007 (2) and 10-24-2007 have been considered. Initialed copies are attached hereto.

Claim Rejections Withdrawn

35 USC § 112

The rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. 112, first paragraph, the specification, while being enabling for methods utilizing VSV for reducing the viability of myelogenous leukemia cell lines *in vitro*, does not provide enablement for the utilization of VSV for the reduction of viability of all hematopoietic tumor cells (either *in vivo* or *in vitro*) is

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withdrawn in light of Applicant's arguments and submissions. A modified enablement rejection is set forth below.

Claim Rejections Maintained

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

The rejection of claims 1 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "administering to the tumor cell a virus" is maintained for reasons of record.

Applicant argues:

1. The skilled artisan would what is claimed and the scope of the claimed subject matter is readily apparent.

Applicant's arguments have been fully considered and deemed non-persuasive.

It is still unclear what is meant by said phrase. Claim 1 recites the phrase "administering to **the** tumor cell **a** virus... It is unclear how this is accomplished when said cell resides (and circulates) within an individual. Moreover, the phrase "to the" can only interpreted as meaning "directly to". Moreover, in the *in vivo* situation, a therapeutic agent is administered to the patient not a particular cell.

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The rejection of claims 24 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "administering interferon to the tumor cell" is maintained for reasons of record.

Applicant argues:

1 The skilled artisan would what is claimed and the scope of the claimed subject matter is readily apparent.

Applicant's arguments have been fully considered and deemed non-persuasive.

New Grounds of Rejection

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-13, 24 and 35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 and 7 of copending Application No. 11/671,498. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

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The claims of the instant application are drawn to methods of reducing the viability of a hematopoietic tumor cell (leukemias etc.) comprising administering to said tumor cell a vesicular stomatitis virus (VSV). The claims of application 10/717,101 are drawn to a method of reducing or eliminating neoplastic (leukemia) cells *ex vivo* from a mixed population of cells wherein said method comprises contacting the cell population with VSV. Hence, both claim sets encompass the reduction of viability (killing/elimination) of tumor cells by the administration of VSV *ex vivo* (i.e. not within the body of an animal). It should be noted that while the claims of application 11/671,498 are drawn to all neoplastic cells and do not explicitly recite the use of the specific hematopoietic tumor cells recited in claims 8-13 in the claimed method, their use was contemplated by the inventors (see paragraph 027 of the specification of application 11/671,498). The skilled artisan in order to practice the methods recited in the claims of application 10/717,101 would necessarily look to the specification to determine what cell types are encompassed by the term "neoplastic cells". Thus it would have been an obvious variation recited methods to use various hematopoietic tumor cells.

Claims 1, 6-13, 24 and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 6-7 of U.S. Patent No. 7,192,580. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to methods of reducing the viability of a hematopoietic tumor cell (leukemia etc.) comprising administering to said tumor cell a vesicular stomatitis virus (VSV). The claims of U.S. Patent 7,192,580 are drawn to a method of reducing or eliminating neoplastic (leukemia) cells *ex vivo* from a mixed population of cells wherein said

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method comprises contacting the cell population with VSV. Hence, both claim sets encompass the reduction of viability (killing/elimination) of tumor cells by the administration of VSV *ex vivo* (i.e. not within the body of an animal). It should be noted that while the claims of application U.S. Patent 7,192,580 are drawn to all neoplastic cells and do not explicitly recite the use of the specific hemapoietic tumor cells recited in claims 8-13 in the claimed method, their use was contemplated by the inventors (see paragraph 027 of the specification of U.S. Patent 7,192,580). The skilled artisan in order to practice the methods recited in the claims of U.S. Patent 7,192,580 would necessarily look to the specification to determine what cell types are encompassed by the term "neoplastic cells". Thus it would have been an obvious variation recited methods to use various hemapoietic tumor cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-13 and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Roberts et al. (WO 99/18799).

Roberts et al. disclose methods utilizing oncolytic viruses to treat (kill) neoplasms wherein said treatment comprises contacting the neoplastic tumor cells with the virus (see abstract). Roberts et al. further disclose that the oncolytic virus can be vesicular stomatitis virus (see page 21 and Table 1) and that VSV was capable of tumor cell specific killing (i.e. VSV selectively infects tumor cells deficient in IFN responsiveness and not "normal" cells)[see page 26, first paragraph]. Moreover, Roberts et al. disclose that their methods could be used to treat leukemias (see page 30, last paragraph). Moreover, it would have been obvious to the skilled artisan to use the method of Roberts et al. to treat the specific leukemias recited in claims 8-13 as Roberts et al. disclose their methods are effective against leukemias generally.

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the VSV strains M1, M2, M3, M4 and M5 are required in order to practice the invention. The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CFR 1.808(a)).

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

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In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

Claims 1, 6-13, 19 and 24-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing attenuated VSV for reducing the viability of hematopoietic tumor cells *in vitro* and the use of attenuated VSV to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization attenuated VSV for the reduction of viability of all types of hemapoietic tumor cells to reduce the viability of a tumor cell in an immunocompetent animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant's arguments to the previous enablement rejection are addressed below to the degree they read on the new rejection and the amended claims.

Applicant argues:

1. McCormick and Pecora use assays and models to test viral therapy whereas the articles cited by the Examiner basically deal with small molecule drugs.
2. Applicant has provided numerous articles related to reducing the viability of a hematopoietic cell by administering VSV.
3. Kelland clearly supports the position that the skilled artisan would conclude that the models and related results described in the specification reasonable correlate with an expected similar result in other animals such as humans.

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4. The Examiner does not describe how Wang et al. relates to the instant invention.

Applicant's arguments have been fully considered and deemed non-persuasive.

5. Gura does not speak to the predictive value of models related to the administration of a virus to a tumor cell.

6. The Examiner has not related Voskoglou-Nomikos et al. to the instant invention.

7. Applicant does not consider the disclosure by Saijo to have particular relevance to the instant invention as Saijo deals with molecular-target based drugs and not the administration of VSV to a tumor cell.

8. Applicant's have shown the application of VSV in several mouse models using hematopoietic tumor cells thus one of skill in the art would expect the results to correlate with results expected in humans.

9. Based on Bibby, one of skill in the art would conclude that methods resulting in the reduction in of hemapoietic tumor cells in a rodent would reasonably correlate with the results in humans.

10. Peterson et al. do not teach that results in xenograft models do not reasonably correlate with clinical results in other animals or humans.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 7, the issues governing the *in vivo* efficacy of a cancer therapy is the same regardless of the specific nature of the therapeutic composition.

With regard to Point 2, the cited references deal with the *in vitro* utilization of VSV or the use of other oncolytic viruses and therefore do not provide support for the full breadth of the claims.

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With regard to Point 3, Kelland, does not advocate the use of a xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not. Moreover, Kelland discloses that the xenograft model is an effective screen for candidates for Phase I clinical trials and contrary to Applicant's assertion does not constitute a predictor of *in vivo* efficacy.

With regard to Point 4, Wang et al. was cited to demonstrate the unpredictability of *in vivo* treatment modalities.

With regard to Point 5, Gura aptly demonstrates the lack of correlation between efficacy demonstrated in xenograft model systems and actual *in vivo* efficacy. Since Applicant is relying on model systems to demonstrate enablement, Gura is germane.

With regard to Point 6, Voskoglou-Nomikos et al. was cited to demonstrate the lack of correlation (i.e. the predictive value) of xenografts. As Voskoglou-Nomikos et al clearly set forth in their abstract, there is no clear correlation between a given xenograft model and the efficacy of a given treatment modality against a given cancer.

With regard to Point 8, taken collectively, there is a preponderance of factual evidence of record that the showing that *in vitro* and xenograft models are not predictive of the *in vivo* efficacy of a cancer treatment modality.

With regard to Point 9, Bibby is very clear that the standard xenograft model is ineffective when he states, "Although this type of model is relatively easy to operate in that it is technically straightforward and generates lots of data it is not necessarily the most relevant to clinical cancer. There are publications that suggest that correlations between xenograft data and

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clinical activity are good, but there are others that give the opposite view. One major drawback of the models that utilize s.c. tumour implants is that they clearly do not produce the primary site of the common human cancers..." (see pages 852-853).

With regard to Point 10, Peterson et al. clearly disclose in the abstract that many agents have shown activity in preclinical models (i.e. *in vitro*, xenografts) but have had minimal activity clinically (see abstract).

On the basis of experimentation performed using an animal model, the specification asserts the invention can be used to treat cancer (hemapoietic). The problem with accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer "vaccines" to attenuate cancer has been met with very little success. In addition to references cited in preceding Office actions, which also describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunization can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer*. 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of “molecularly-targeted”, largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host’s (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, “it is premature and too much a ‘leap of faith’ to jump directly from *in vitro* activity testing (or even *in silico* methods) to Phase I clinical trials (via preclinical regulatory toxicology)” (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Moreover, as noted in preceding Office action, Gura (of record) teaches that although researchers had hoped that xenografts would prove to be better models for studying cancer in

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humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, “the results of xenograft screening turned out to be not much better than those obtained with the original models”. Gura states that as a result of their efforts, “ ‘[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs’ ”.

With further regard to the predictive value of various different preclinical models, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; 95 (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Applicant has argued that the use of xenografts in mice for evaluating therapeutic efficacy of drugs for treating humans is well established; agreeably the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results

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to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen. Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that “[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials” (abstract). Furthermore, Schuh discloses, “[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice” (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer*. 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such “orthotopic” models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer*. 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, “have led to reasonable skepticism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that

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will have important clinical utility” (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, “The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.” “The “amount of guidance or direction” refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling” (MPEP 2164.03). **The MPEP further states that physiological activity can be considered inherently unpredictable.** Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the

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specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of reducing the viability of hemapoietic tumor cells by administering an attenuated strain of VSV to said melanoma tumor cells. Said melanoma tumor cells can optionally be leukemia cells or myeloma (claims 6-13), have no PKR activity and/or have no STAT1 activity (claim 19). Said VSV virus can be unable to inactivate tumor cell PKR activity (claim 25), or may constitute strains M1-M5 (claims 27-31, respectively). Said method encompasses methods of "treating" tumor cells which reside in a

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mammalian host. Said method may include the optional administration of interferon prior to the administration of the virus (claims 24 and 37).

Breadth of the claims: The claims are extremely broad in that they encompass literally any attenuated VSV strain. Moreover, the instant claims encompass both *in vivo* and *in vitro* applications. It should be noted that all the instant claims read on the *in vivo* treatment of hemapoietic tumor cells in humans.

Guidance of the specification/The existence of working examples: To use the invention as claimed one must be able to differentially infect a susceptible tumor cell resulting in a reduction in said cell's viability. While the specification provides great detail on the susceptibility of different cell types to VSV and the protective effect of alpha interferon against VSV infection, the specification is silent on the what viruses other than VSV would induce the claimed anti-tumor effect. Additionally, the instant claims are drawn to all forms of hematopoietic tumor cells, while the specification has demonstrated only two leukemia cell lines (MD7E and L1210), a couple of AML cell lines OCI/AML3 and AML5, one CML cell line (K-562) and a T-cell leukemia (MOLT-4) that are that are susceptible to VSV infection. VSV was shown to reduce the viability of only the AML, CML and T-cell leukemia cell lines.

The specification is silent on what receptor is utilized by VSV (or any other virus) for cell entry or which cell types would be able to support a productive viral infection making it difficult to determine if a given tumor cell would be susceptible to the oncolytic properties of VSV or be used as a suitable delivery vehicle. Moreover, the specification is equally silent on what other melanoma tumor cell types are killed by VSV infection. The invention seems to be predicated on

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the susceptible tumor cells lacking PKR activity, but the specification is silent on which melanoma tumor cells lack said function.

State of the art: At the time of applicants' invention the art of using oncolytic viruses to treat melanomas was underdeveloped. While the use of oncolytic viruses has been known in the art for decades, said oncolytic viruses were limited, to viruses that would be considered human pathogens.

Predictability of the art and the amount of experimentation necessary:

People of skill in the art require evidence that a benefit can be derived by the therapeutic application of a given substance; however, a survey of the relevant art does not indicate that substances such as those claimed provide such benefit. The instant specification fails to provide significant direction on which viruses, if any, are capable of eliciting a therapeutic response (tumor cell death) when administered to an immunocompetent subject in need. Moreover, the specification is equally silent on how said viruses are to be administered to said subject. Jain discloses known barriers to the delivery of drugs into solid tumors (Scientific American Vol. 271 No. 1, pages 58-65, July 1994). Impediments to drug delivery include: (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61) and (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1). Consequently, the method of administration would vary depending on the tumor

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cell type and location of said tumor. Unfortunately, the specification fails to provide guidance to how a given virus should be administered when treating a given hemapoietic cancer. The specification illustrates this point on page 33 where it states that PKR-/- mice were killed with VSV by several routes of infection but that these mice were not affected by intravenous injections of the virus. Moreover, there is a marked difference in the efficacy of delivering a therapeutic agent to a solid tumor cell as opposed to a leukemia cell.

The specification teaches how to use VSV to reduce the viability of melanoma cell lines injected into immunodeficient mice to form xenographs and provides *in vitro* data showing effects of VSV infection on a several hematopoietic cell lines (either with or without alpha interferon). However, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to "treat" hematopoietic tumor cells, although *in vivo* use is clearly encompassed by the claims. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* and xenograft data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals without undue experimentation. Moreover, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that

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may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature 'for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Additionally, it should be noted that Example 25 is insufficient to provide enablement for the full breadth of the instant claims. Firstly, the xenographs utilized in Example 25 (on page 50 of the specification), comprise a melanoma derived cell line (SK-MEL3). Secondly, said example only utilizes two of the five VSV mutants disclosed in the instant specification suggesting that the anti-tumor effect of the disclosed VSV mutants is unpredictable. Thirdly, the instant claims are drawn to use of VSV to reduce the viability of all types of melanoma tumor cells whereas Example 25 demonstrates only that two mutated VSV viruses can reduce the viability of cell-line based xenographs in immunodeficient mice. This cannot be extrapolated to the use of wild-type (non-mutated) VSV against established tumors in an immunocompetent animal. Gura (Science, Vol. 278, 1997 pages 1041-1042) teach that xenographs are not good models for determining the efficacy of a treatment modality since “xenograft tumors don’t behave like naturally occurring tumors in humans” (see column 2). Gura illustrates the lack of correlation between efficacy in xenograft model systems and *in vivo* efficacy in humans when she states that the use of xenografts led them to discover “compounds that were good mouse drugs rather than good human drugs” (see the bottom of column 2 on page 1041).

Consequently, the specification while being enabling for methods utilizing VSV for reducing the viability of hematopoietic tumor cells *in vitro* and the use of VSV to reduce the viability of tumor cell based xenografts in immunodeficient mice, does not reasonably provide enablement for the utilization VSV for the reduction of viability of a hematopoietic tumor cell in an immunocompetent animal. The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866.

The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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PRIMARY EXAMINER

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